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(54) Title: NEW FORMULATION FOR INHALATION HAVING A POURED BULK DENSITY OF 0.28 TO 0.38 G/ML, A PROCESS FOR PREPARING THE FORMULATION AND THE USE THEREOF

(57) Abstract

A dry powder composition comprising one or more potent pharmaceutically active substances and a carrier substance, all of which are in finely divided form, wherein the formulation has a poured bulk density of from 0.28 to 0.38 g/ml is useful in the treatment of respiratory disorders.

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NEW FORMULATION FOR INHALATION HAVING A POURED BULK DENSITY OF 0.28 TO 0.38 G/ML, A PROCESS FOR PREPARING THE FORMULATION AND THE USE THEREOF

*Field of the Invention*

The present invention provides a new pharmaceutical formulation, its preparation and its use.

*Background to the Invention*

Potent drugs for administration by inhalation are generally formulated in association with carriers such as lactose because of the problem of preparing accurate doses. When such drugs are diluted, variations in the weight of the formulation result in a smaller drug dosage variation rate compared with when they are not diluted. These formulations have generally consisted of coarse particles of the carrier with fine particles of the drug, which combination is generally known as an ordered mixture.

The invention provides an improved formulation which, in systems designed to imitate inhalation has been found to give an improved dispersion of the drug.

*Description of the Invention*

According to the invention there is provided a dry powder composition comprising one or more potent pharmaceutically active substances and a carrier substance, all of which are in finely divided form, wherein the formulation has a poured bulk density of from 0.28 to 0.38 g/ml, preferably from 0.30 to 0.36 g/ml.

The poured bulk density according to the present invention is measured using known techniques, for example those described in "Powder testing guide: Methods of measuring the physical properties of Bulk powders" L. Svarovsky, Elsevier Applied Science 1987, pp 84-86.

A potent pharmaceutically active substance suitable for use in the invention is, for example, an antiarrhythmic drug, tranquiliser, cardiac glycoside, hormone, hypertensive drug, antidiabetic or anticancer drug, sedative or analgesic drug, antibiotic, antirheumatic drug, immunotherapy, antifungal or antihypotension drug, vaccine, antiviral drug, protein (e.g. insulin), peptide, vitamin, or a cell surface receptor blocker. It is preferably a glucocorticosteroid, particularly one which is metabolised rapidly, for example beclomethasone dipropionate (BDP), beclomethasone monopropionate (BMP), flunisolide, triamcinolone acetonide, fluticasone propionate, ciclesonide, budesonide, rofleponide or derivatives thereof, momethasone, tipredane, RPR 106541 and/or a β2-agonist such as terbutaline, salbutamol, formoterol, salmeterol, TA 2005, pircumarol or a pharmaceutically acceptable salt thereof; and/or a prophylactic agent such as sodium chromoglycate or nedocromil sodium.

Suitable physiologically acceptable salts include acid addition salts derived from inorganic and organic acids, for example the chloride, bromide, sulphate, phosphate, maleate, fumarate, tartrate, citrate, benzoate, 4-methoxybenzoate, 2- or 4-hydroxybenzoate, 4-chlorobenzoate, p-toluenesulphonate, methanesulphonate, ascorbate, acetate, succinate, lactate, glutarate, gluconate, tricarballylate, hydroxynaphthalene-carboxylate or oleate salts or solvates thereof.

The carrier substance is preferably a mono-, di- or polysaccharide, a sugar alcohol or another polyol. Suitable carriers are, for example, lactose, glucose, raffinose, melezitose, lactitol, maltitol, trehalose, sucrose, mannitol; and starch. Lactose is particularly preferred, especially in the form of its monohydrate.

The ingredients of the formulation according to the invention must both be in a finely divided form, i.e. their mass median diameter should generally be less than 10 μm, preferably from 1 to 7 μm, as measured by a laser diffraction instrument or a coulter counter. The ingredients may be produced in the desired particle size using methods known to those of skill in the art, e.g. milling, micronisation or direct precipitation.

The combination of budesonide and formoterol is particularly preferred. Formoterol is preferably used in the form of its fumarate, especially the dihydrate.

When the one or more potent pharmaceutically active substances used in the invention are formoterol and budesonide, the molar ratio of formoterol to budesonide in the composition of the invention is preferably from 1:2500 to 12:1, more preferably from 1:555 to 2:1, most preferably from 1:133 to 1:6. The composition according to the invention is preferably formulated to provide a daily dose of formoterol of from 2 to 120 nmol (more preferably from 7 to 70 nmol). When formoterol is used in the form of formoterol fumarate dihydrate, the composition is preferably formulated to provide a daily dose of formoterol fumarate dihydrate of from 1 to 50 μg, more preferably from 3 to 30 μg. The composition according to the invention is preferably formulated to provide a daily dose of budesonide of from 45 to 2200 μg, more preferably from 65 to 1700 μg.

More preferably the composition of the invention comprises, as a unit dose, 6μg of formoterol fumarate dihydrate and 100μg of budesonide, or 4.5μg of formoterol fumarate dihydrate and 80μg of budesonide, either of which can be administered up to four times a day. Alternatively the composition of the invention comprises, as a unit dose, 12μg of formoterol fumarate dihydrate and 200μg of budesonide, or 9μg of formoterol fumarate dihydrate and 160μg of budesonide, either of which is administered once or twice a day.

Most preferably the composition used in the invention comprises, as a unit dose, 6μg of formoterol fumarate dihydrate and 200μg of budesonide, or 4.5μg of formoterol fumarate dihydrate and 160μg of budesonide, either of which is administered up to four times a day. Alternatively the composition of the invention comprises, as a unit dose, 12μg of formoterol fumarate dihydrate and 400μg of budesonide, or 9μg of formoterol fumarate dihydrate and 320μg of budesonide, either of which is administered once or twice a day.

According to the invention there is further provided a process for preparing a composition according to the invention which comprises

(a) micronising the one or more potent pharmaceutically active substances and the carrier substance;

(b) optionally conditioning the product; and

(c) spheronizing until the desired bulk density is obtained.

The process preferably further comprises a low energy remicronisation step after step (b).

The formulation according to the invention may be made by conventional techniques known *per se*. Such production processes generally comprise micronising the ingredients to the required size, removing any amorphous areas on the particles obtained by, for example, the methods described in WO 92/18110 or WO 95/05805 and then agglomerating, spheronising and sieving the powder obtained. The size of the agglomerates obtained is preferably in the range of from 100 to 2000 μm, more preferably from 100 to 800 μm. The bulk density of the formulation produced may be adjusted by varying the components and the process empirically, for example the bulk density can be increased by lengthening the time in which the particles are tumbled in a spheronising device.

In solid-solid mixing, one of the most important features is to ensure content uniformity. The major problem encountered in the powder mixing of fine powders is the inability of mixers to break down powder agglomerates. It has been found that a remicronisation step after the conditioning step of the fine powder with low energy input is advantageous. It should generally be carried out using enough energy to break down powder agglomerates but not with so much energy that the size of the particles themselves is affected. Such a step gives a composition wherein the active substance and carrier substance are substantially uniformly distributed, having for example a relative standard deviation of less than 3% (preferably less than 1%) and does not disturb the crystallinity of the fine particles.

The formulation according to the invention may be administered using any known dry powder inhaler, for example the inhaler may be a single or a multi dose inhaler, and may be a breath actuated dry powder inhaler, for example Turbuhaler (trade mark). The invention further provides use of a composition according to the invention in the manufacture of a medicament for use in therapy. The composition according to the invention is useful in the treatment of respiratory disorders, particularly asthma. The invention also provides a method of treating a patient suffering from a respiratory disorder which comprises administering to the patient a therapeutically effective amount of a composition according to the invention.

The invention is illustrated, but not limited, by reference to the following Examples.

*Example 1*

0.0315 Parts of formoterol fumarate dihydrate and 2.969 parts of lactose monohydrate are mixed in a tumbling mixer (Turbula) to an evenly distributed mixture, whereafter the mixture is micronised in a spiral jet mill using a pressure and feeding rate suitable to obtain a particle size of less than 3 μm (mass median diameter as measured by a coulter counter). The micronised particles were then treated using the method disclosed in WO 95/05805 to remove amorphous regions in their crystal structure. The powder was then agglomerated by feeding the powder into a twin screw feeder (K-Tron), sieving in an oscillating sieve (0.5 mm mesh size), spheronising in a rotating pan with a peripheral speed of 0.5m/s for 4 minutes and then sieving again using the same sieve, then spheronising once more for 6 minutes before final sieving (mesh size 1.0 mm) giving a powder with a bulk density of 0.32g/ml.

*Example 2*

Example 1 was repeated but the powder was remicronised in a spiral jet mill at a lower pressure (about 1 bar) after micronisation and conditioning such that the step of treating the

particles in the manner described in WO 95/05805 was not required giving a powder with a bulk density of 0.32 g/ml.

*Example 3*

9 Parts of budesonide and 91 parts of lactose monohydrate were micronised separately in a spiral jet mill at a pressure of about 6-7 bars to give a particle size of less than 3 μm before being mixed thoroughly in a Turbula mixer. Before mixing, the lactose monohydrate powder was conditioned according to the method described in WO 95/05805. The mixture was remicronised in a spiral jet mill at a pressure of only about 1 bar to obtain a uniform mixture. The powder was then agglomerated and spheronised as described in Example 1 to obtain a bulk density of 0.35 g/ml.

*Example 4*

60 Parts of terbutaline sulphate were micronized to a mass medium diameter of less than 2 μm in a Alpin mill 100AFG and thereafter conditioned according to the method described in US 5562923. 40 Parts of lactose monohydrate were micronized (Alpin mill 100AFG) down to a mass medium diameter of less than 3 μm and thereafter conditioned according to the method described in WO 95/05805. The micronized and conditioned terbutaline sulphate and lactose monohydrate were mixed thoroughly in a Turbula mixer. The mixture was remicronised in a spiral jet mill at a pressure of only about 1 bar to obtain an evenly distributed mixture. The powder was then agglomerated and spheronised as described in Example 1 to obtain a bulk density of 0.28 g/ml.

*Example 5*

Example 4 was repeated with 30 parts of terbutaline sulphate and 70 parts of lactose monohydrate to give a powder with a bulk density of 0.31 g/ml.

*Example 6*

5.2 Parts of formoterol fumarate dihydrate and 896.8 parts of lactose monohydrate were mixed in a tumbling mixer to an evenly distributed mixture, whereafter the mixture was micronised in a spiral mill using a pressure and feeding rate suitable to obtain a particle size of less than 3 μm (mass medium diameter as measured by a coulter counter). The micronised particles were then treated using the method described in WO 95/05805 to remove amorphous regions in their crystal structure. 98 parts of micronised budesonide were added and the mixture was remicronized at a lower pressure in a spiral jet mill to a homogenous mixture. The powder was then agglomerated by feeding into a screw feeder (K-Tron), sieved in an ocillating sieve (0.5 mm mesh size), spheronised in a rotating pan with a speed of 23 rpm for 10 minutes, then sieved again (0.5 mm mesh size), spheronised once more before final sieved (0.8 mm mesh size) to give a powder with a bulk density of 0.34 g/ml.

*Example 7*

Example 6 was repeated with identical conditions but using 5.2 parts of micronized formoterol fumarate dihydrate, 798.8 parts of micronized lactose monohydrate and 196 parts of micronized budesonide. The bulk density obtained was 0.34 g/ml.

*Claims*

1. A dry powder composition comprising one or more potent pharmaceutically active substances and a carrier substance, all of which are in finely divided form, wherein the formulation has a poured bulk density of from 0.28 to 0.38 g/ml.

2. A composition according to claim 1 wherein the one or more potent pharmaceutically active substances are budesonide and formoterol.

3. A composition according to claim 1 or 2 wherein the bulk density is from 0.30 to 0.36 g/ml.

4. A composition according to claim 1, 2 or 3 wherein the active substance and carrier substance are substantially uniformly distributed.

5. A composition according to any one of claims 1 to 4 for use in the treatment of a respiratory disorder.

6. A process for preparing a composition according to claim 1 which comprises

(a) micronising the one or more potent pharmaceutically active substances and the carrier substance;

(b) optionally conditioning the product; and

(c) spheronizing until the desired bulk density is obtained.

7. A process according to claim 6 which comprises a low energy remicronisation step after step (b).

8. Use of a composition according to any one of claims 1 to 4 in the manufacture of a medicament for use in therapy.

9. A method of treating a patient suffering from a respiratory disorder which comprises administering to the patient a therapeutically effective amount of a composition according to any one of claims 1 to 4.

# INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 98/00040

A. CLASSIFICATION OF SUBJECT MATTER

IPC6: A61K 9/72, A61K 31/165, A61K 31/58
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC6: A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

WPI, USPATFULL, CAPLUS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| X | US 5551489 A (EVA A. C. TROFAST ET AL), 3 Sept 1996 (03.09.96), column 2, line 8 - line 15 | 1-9 |
| X | US 4590206 A (RAYMOND B. FORRESTER ET AL), 20 May 1986 (20.05.86), column 4, line 15 - line 21; column 4, line 46 - line 47 | 1-9 |

☐ Further documents are listed in the continuation of Box C. ☒ See patent family annex.

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| Date of the actual completion of the international search | Date of mailing of the international search report |
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| 13 May 1998 | 19 -05- 1998 |
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# INTERNATIONAL SEARCH REPORT

Inte...ational application No.
PCT/SE 98/00040

**Box I** Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 9
because they relate to subject matter not required to be searched by this Authority, namely:

Remark: Claim 9 is directed to method of treatment of the human or animal body by therapy methods practised on the human or animal body/Rule 39.1(iv). Nevertheless, a search has been executed for this claims. The search has been based on the alleged effects of the composition.

2. [ ] Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

**Box II** Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

# INTERNATIONAL SEARCH REPORT

Information on patent family members

29/04/98

International application No.
PCT/SE 98/00040

| Patent document cited in search report | Publication date | Patent family member(s) | Publication date |
|---|---|---|---|
| US 5551489 A | 03/09/96 | AU 7826194 A | 01/05/95 |
| | | CZ 9600942 A | 12/06/96 |
| | | EP 0721331 A | 17/07/96 |
| | | FI 961430 A | 29/03/96 |
| | | HU 74519 A | 28/01/97 |
| | | HU 9600821 D | 00/00/00 |
| | | IL 111080 D | 00/00/00 |
| | | NO 961290 A | 29/03/96 |
| | | PL 313765 A | 22/07/96 |
| | | SE 9303214 D | 00/00/00 |
| | | SE 9304271 D | 00/00/00 |
| | | WO 9509615 A | 13/04/95 |
| | | ZA 9407533 A | 03/04/95 |
| | | AU 679789 B | 10/07/97 |
| | | BR 9407686 A | 04/02/97 |
| | | IL 113023 D | 00/00/00 |
| | | JP 9504224 T | 28/04/97 |
| | | SE 9400896 D | 00/00/00 |
| | | SK 39196 A | 04/06/97 |
| | | CN 1132476 A | 02/10/96 |
| US 4590206 A | 20/05/86 | AU 540826 B | 06/12/84 |
| | | AU 8635582 A | 10/02/83 |
| | | BE 893912 A | 24/01/83 |
| | | CA 1187415 A | 21/05/85 |
| | | CH 657273 A,B | 29/08/86 |
| | | DK 159716 B,C | 26/11/90 |
| | | DK 325982 A | 25/01/83 |
| | | EP 0072046 A,B | 16/02/83 |
| | | SE 0072046 T3 | |
| | | FI 822548 A | 25/01/83 |
| | | FR 2510405 A | 04/02/83 |
| | | GB 2105189 A,B | 23/03/83 |
| | | HK 10088 A | 12/02/88 |
| | | JP 4068285 B | 02/11/92 |
| | | JP 58059914 A | 09/04/83 |
| | | LU 84291 A | 07/02/83 |
| | | PT 75310 B | 29/11/85 |
| | | US 5260306 A | 09/11/93 |
| | | ZA 8205222 A | 25/05/83 |

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so certify that the attached copy of the request for grant of a Patent (Form 1/77) bears an ndment, effected by this office, following a request by the applicant and agreed to by the ptroller-General.

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2. Patent application number *(The Patent Office will fill in this ...)* 0219513.9 21 AUG 2002

3. Full name, ... postcode of the or of each applicant *(underline all surnames)*

Norton Healthcare Limited
Albert Basin
Royal Docks
London
E16 2QJ
United Kingdom

Patents ADP number *(if you know it)* 61882210003

If the applicant is a corporate body, give the country/state of its incorporation United Kingdom

4. Title of the invention

Inhalation Compositions Including Coarse Carrier

5. Name of your agent *(if you have one)*

ELKINGTON AND FIFE

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PM 3/3/5

Patents ADP number *(if you know it)* 67004

6. If you are declaring priority from one or more earlier patent applications, give the country and the date of filing of the or each of these earlier applications and *(if you know it)* the or each application number

| Country | Priority application number *(if you know it)* | Date of Filing *(day/month/year)* |
|---|---|---|
| N/A | | |

7. If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application

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|---|---|
| N/A | N/A |

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*b) there is an inventor who is not named as an applicant, or*
*c) any named applicant is a corporate body.*

*See note (d))*

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| Translations of priority documents | - |
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| Request for preliminary examination and search *(Patents Form 9/77)* | - |
| Request for substantive examination *(Patents Form 10/77)* | - |
| Any other documents *(please specify)* | - |

11. I/We request the grant of a patent on the basis of this application.

Signature: Elkington and Fife

Date: 21 August 2002

12. Name and daytime telephone number of person to contact in the United Kingdom

Dr Gordon Wright
01732 458881

# INHALATION COMPOSITIONS INCLUDING COARSE CARRIER

This invention relates to dry powder inhalation compositions, their preparation and use. In particular, it is concerned with formulations of the medicament formoterol and pharmaceutically acceptable derivatives thereof mixed with particulate lactose.

In order to be able to be inspired into the key target sites in the lungs of patients, inhalation drugs are typically provided in micronized form with average particle sizes of up to 10 microns. A number of devices have been developed for assisting the delivery of such medicaments into the lungs of patients. In one sort of device, a dry powdered inhaler (DPI) device, the medicament to be inhaled is dispensed into an air stream produced by the inspiratory action of the patient. A large number of such devices have been developed. The device may be a single dose device (eg wherein drug is dispensed from a pre-metered dosage means such as a capsule) or multidose (where the drug is stored in a reservoir and then metered prior to dispersal in the air stream or where the drug is pre-metered and then stored in multiple dosage packs such as blisters). In many (but not all) DPI devices, the particulate drug is mixed with an excipient powder of larger average particle size and the drug particles are blended with the excipient to create a generally homogenous mixture. The larger particle size of the excipient results in the powder mixture being flowable, and the homogeneity of the mixture enables it to be metered into accurately measurable doses. This is of particular importance when only very small quantities of the drug are required in a dose. Excipient powders of this kind, pharmaceutical powder compositions for inhalation utilising such excipients are described, for example, in US Patent 3 957 965.

The accurate metering of highly potent inhalable drugs causes particular problems, as the quantity of medicament in the composition relative to that of the carrier is likely to be particularly small. (Less than 1 part of drug to 50 parts of carrier). One such medicament is formoterol which is often administered to patients at a dose of less than 60 micrograms; doses may be as small as 6 micrograms. We have now found dry powder inhalation compositions of formoterol which are easier to handle than previously described compositions. In addition, the composition can be readily filled into reservoir containing multidose DPI devices, such as the multidose DPI (MDPI) device described in WO 92/10229. In addition, the such compositions can be

accurately metered and give better dispersions when dispensed from such devices, then previously described compositions. Certain compositions may also be more stable.

According to the invention, we provide a dry powder inhalation composition comprising particulate formoterol or a pharmaceutically acceptable derivative thereof as active ingredient and particulate lactose, wherein the lactose has a volume median diameter (VMD) of between 80 and 120 microns, 100% by weight of the lactose particles are less than 250 microns, between 80 and 96 % by weight are less than 150 microns, between 33 and 55 % by weight are less than 90 microns and between 8 and 25 % by weight are less than 5 microns.

We prefer compositions in which between 18 and 37 %, more preferably between 18.5 and 36.5 %, by weight of the lactose has a particle size less than 60 microns. A particular range that may be mentioned is 18.9 to 36.1 by weight.

We prefer compositions wherein between 15 and 35 % by weight, more preferably between 15.5 and 34.5 % by weight, of the lactose has a particle size less than 30 microns. A particular range that may be mentioned is between 16 and 34 % by weight.

We prefer a composition wherein between 14 and 32 % by weight, more preferably 14.5 and 31.5 % by weight of the lactose has a particle size less than 15 microns. A particularly preferred range that may be mentioned is between 15 and 31 %.

We prefer compositions wherein between 13 and 30 % by weight, more preferably between 13.5 and 29.0 % by weight, of the lactose has a particle size less than 10 microns. A particularly preferred range is between 14.2 and 28.5 %.

We prefer compositions wherein between 34 and 52 % by weight of the lactose has a particle size less than 90 microns, more preferably between 34.8 and 50.8 % by weight.

We prefer compositions in which between 8.0 and 24.5 % by weight, more particularly between 8.0 and 24.0 % by weight of the lactose has a particle size less than 5 microns.

The compositions of the present invention may be used in the treatment of chronic obstructive pulmonary disease.

The active ingredient may be in any isomeric form or mixture of isomeric forms, for example a pure enantiomer, particularly the R, R-enantiomer, a mixture of enantiomers, a racemate or a mixture thereof. Pharmaceutically acceptable derivatives of formoterol include pharmaceutically acceptable salts, in particular acid addition salts with inorganic acids such as hydrochloric acid, hydrobromic acid, sulphuric or phosphoric acid. The salt may also be with an organic acid such as acetic, succinic, maleic, furmaric, citric, tartaric, lactic or benzoic. The active ingredient and pharmaceutically acceptable derivatives thereof may exist in the form of a solvate, in particular a hydrate. A preferred form of active ingredient for use in the invention is formoterol fumarate, especially formoterol fumarate di-hydrate, conveniently in its racemic form. Formoterol, salts and hydrates thereof and salt hydrates thereof as described above may be prepared by known methods, for example as described in US 3 994 974 or US 5 684 199.

In general, the active ingredient is present in the dry powder composition at an amount which is less than 10 %, preferably less than 2 % and most preferably less than 1 %. The actual amount of active ingredient in the composition will depend to a large extent on the nature of the dry powder inhaler and the quantity of composition that is metered individual dose. Where a large dose of composition is metered, the proportion of formoterol in the dose will be reduced. Particularly dilute compositions are disclosed in WO 01/39745, for example 0.02 % by weight.

The mean particle diameter of the active ingredient is preferably up to 10 microns, more preferably up to 5 microns especially from 1 to 5 microns. The particle size of the active ingredient can be reduced to the desired level by conventional means, for example by grinding in a mill for example an air jet, ball or vibrator mill, by sieving, by crystallisation, by spray-drying or by lyophilisation.

The desired particle size distribution of the lactose may be prepared in a similar way. However, it is preferable to prepare the lactose by blending two or more portions of

previously classified lactose, for example a fine blend of lactose, in which the mean particle diameter is less than 10 microns and a portion in which the mean particle diameter is relatively coarse. A characteristic coarse lactose will be that supplied as classified lactose that is collected by a mesh with mesh size of 90 microns after passing through a mesh with mesh size of 150 microns.

The dry powder composition may be metered and filled into capsules, eg gelatine or hydroxypropyl methol cellulose capsules such that the capsule contains a unit dose of active ingredient.

Doses of active ingredient to be held in accordance with the invention, may be in general from 1 to 60 micrograms. When the active ingredient is formoterol fumarate dihydrate, the dose may be, for example, from 6 to 54 micrograms. Preferred doses are from 6 to 24 micrograms, especially the unit doses of 6 micrograms, 12 micrograms and 24 micrograms. These doses may be administered once or twice daily.

When the dry powder is in a capsule containing a unit dose of active ingredient, the total amount of composition will depend on the size of the capsules and the characteristics of the inhalation device with which the capsules are being used. However, characteristic total fill weights of dry powder to per capsule are between 1 and 25 mg eg 5, 10, 15 or 20 mg.

Alternatively, the dry powder composition according to the invention may be filled into the reservoir of a multidose dry powder inhaler, for example of the kind illustrated in WO 92/10229.

Compositions according to the invention may be readily prepared by blending the required amount of active ingredient with the required amount of particulate lactose of the desired particle size distribution.

Preferably, the lactose is alpha lactose monohydrate.

**Example 1**

0.265 grams of formoterol (as the fumarate dihydrate salt) was blended with 99.735 grams of lactose that has a particle size distribution within the range as shown in Table 1. The lactose was prepared by blending a mixture of 90 to 150 micron lactose (95%) with microfine lactose having a VMD of 7.5 microns (5%). The formoterol lactose blend was filled into the reservoir of a dry powder inhaler of the type illustrated in WO 92/10229.

8 such batches were prepared with the following particle sizes:

**Table 1**: Particle size distribution for the formoterol lactose

| Parameters | Mean | Range |
|---|---|---|
| VMD | 97 μm | 89-110 μm |
| GSD | 4.4 | 2.2-4.9 |
| | | |
| <5 μm | 13.1% | 8.0%-24.0% |
| < 10 μm | 21.6% | 14.2%-28.5% |
| < 15 μm | 24.5% | 15.0%-31.0% |
| < 30 μm | 26.5% | 16.0%-34.0% |
| < 60 μm | 29.6% | 18.9%-36.1% |
| < 90 μm | 44.5% | 34.8%-50.8% |
| < 150 μm | 87.7% | 83.9%-93.5% |
| < 174 μm | 96.0% | 93.8%-98.9% |
| < 250 μm | 100% | 100% |

Typical particle size distribution of a lactose blend is shown in Fig. 1.

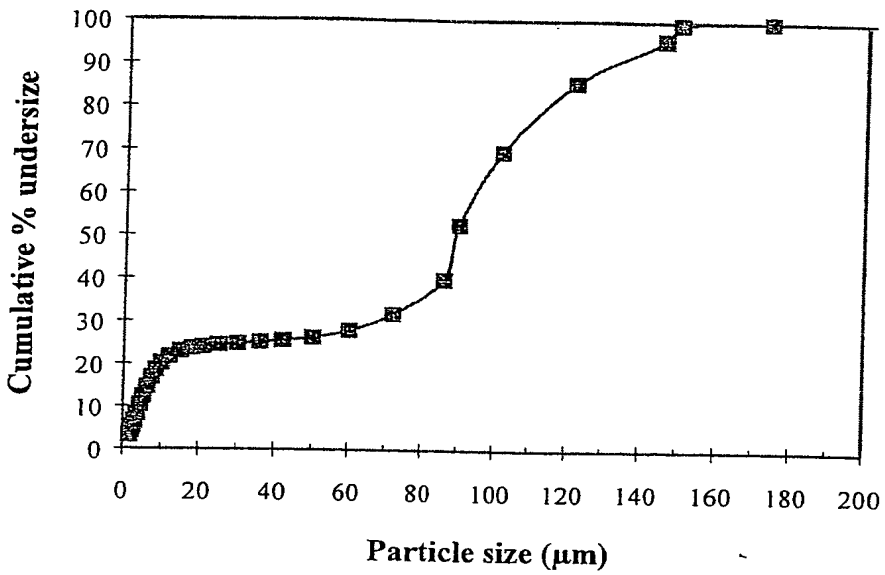


Figure 1. The particle size distribution of a batch of lactose

## IN-VITRO COMPARISON STUDIES.

In order to measure the performance of the product thus developed, a study was undertaken which compared the drug delivery and deposition properties of the multidose dry powder inhaler illustrated in WO 92 10229 (hereinafter referred to as the Ivax MDPI) with the Oxis Turbohalers®. The Ivax MDPIs and Oxis Turbohaler were tested under the same conditions specified in European Pharmacopoeia (2001). The drug per actuation (DPA) was measured using a dose unit sampling apparatus whilst fine particle dose (FPD) and fine particle fraction (FPF) were measured using a 5-stage liquid impinger.The Turbohaler (Fig. 2) showed a much larger variation in DPA than the Ivax MDPI (Fig. 3). The mean DPA from three Turbohalers with label claim of 6 μg was 3.9 μg, suggesting that a large portion (over 30%) of the drug was not released from the device. The mean DPA from three Ivax MDPIs was 5.3 μg, which was within 80-120% label claim (6 μg). The three Turbohaler devices showed an RSD of 27.8% for the DPA values which was more than twice the value (11.9%) of the Ivax MDPI. Therefore, the Ivax MDPI is more consistent in the delivery of the drug than the Turbohaler.

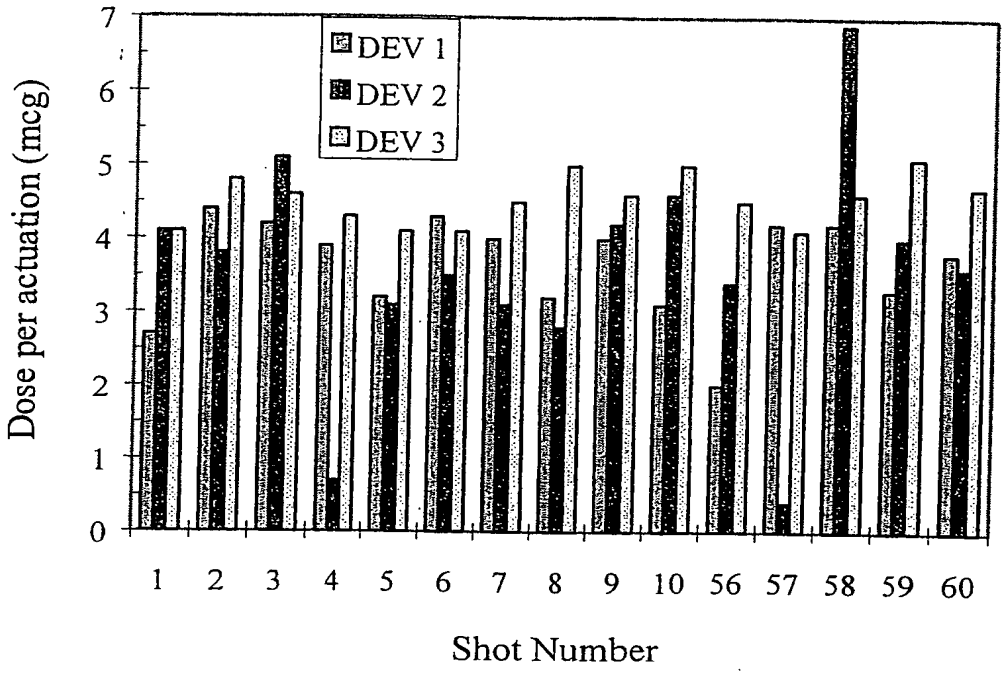


Figure 2. The drug per actuation from Oxis Turbohaler with a label claim of 6 μg formoterol (Batch ZE226)

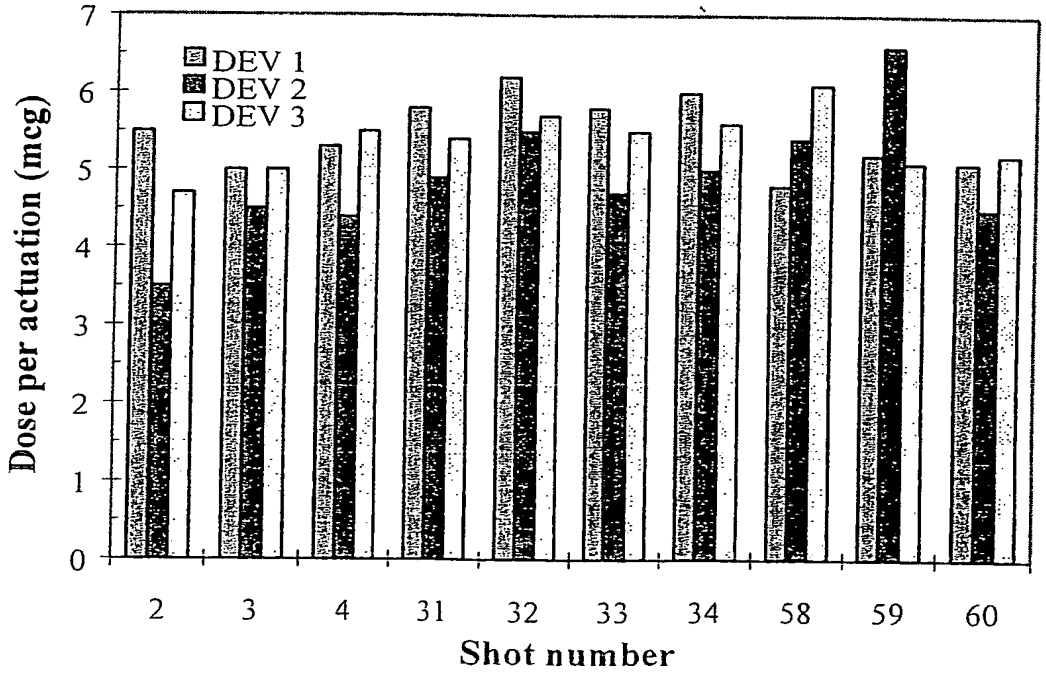


Figure 3. The drug per actuation from Ivax MDPI with a label claim of 6 μg.

**Table 2**. Deposition profiles of formoterol Oxis Turbohaler and Ivax MDPI (The label claim of both devices was 6 μg)

| | **Ivax MDPI** | | | **Oxis Turbohaler batch ZE 226** | | |
|---|---|---|---|---|---|---|
| Actuations 7-26 | Device 1 | Device 2 | Device 3 | Device 1 | Device 2 | Device 3 |
| IND. PORT (μg) | 1.07 | 1.12 | 0.98 | 1.00 | 1.00 | 1.10 |
| STAGE 1(μg) | 1.95 | 1.94 | 1.94 | 0.20 | 0.10 | 0.20 |
| STAGE 2(μg) | 0.39 | 0.24 | 0.29 | 0.10 | 0.10 | 0.20 |
| STAGE 3(μg) | 0.82 | 0.77 | 0.83 | 0.60 | 0.70 | 0.90 |
| STAGE 4(μg) | 0.83 | 0.90 | 0.82 | 0.90 | 0.90 | 1.10 |
| STAGE 5(μg) | 0.73 | 0.78 | 0.65 | 0.70 | 0.70 | 0.90 |
| **RD (μg)** | **5.79** | **5.75** | **5.51** | **3.50** | **3.50** | **4.20** |
| **FPD (μg)** | **2.60** | **2.50** | **2.40** | **2.30** | **2.30** | **2.80** |
| FPF (% RD) | 45 | 43 | 44 | 66 | 66 | 67 |
| **FPF (% LC)** | **43** | **42** | **40** | **38** | **38** | **47** |
| Actuations 37-56 | | | | | | |
| IND. PORT (μg) | 0.93 | 0.83 | 0.85 | 1.10 | 0.90 | 0.70 |
| STAGE 1(μg) | 2.16 | 2.08 | 2.15 | 0.30 | 0.20 | 0.20 |
| STAGE 2(μg) | 0.25 | 0.27 | 0.26 | 0.10 | 0.10 | 0.20 |
| STAGE 3(μg) | 0.64 | 0.72 | 0.67 | 0.70 | 0.60 | 0.50 |
| STAGE 4(μg) | 0.71 | 0.84 | 0.76 | 0.90 | 0.80 | 0.60 |
| STAGE 5(μg) | 0.60 | 0.76 | 0.71 | 0.70 | 0.70 | 0.50 |
| **RD (μg)** | **5.29** | **5.50** | **5.40** | **3.90** | **3.40** | **2.60** |
| **FPD (μg)** | **2.10** | **2.40** | **2.20** | **2.40** | **2.20** | **1.60** |
| FPF (% RD) | 40 | 44 | 41 | 62 | 65 | 62 |
| **FPF (% LC)** | **35** | **40** | **37** | **40** | **37** | **27** |

Note: RD is the total recovered dose from the impinger; LC is label claim and IND. Port stands for Induction Port.

No significant difference was found in the fine particle dose (FPD) of formoterol from the Ivax MDPI (2.37 ± 0.19 μg) and the Oxis Turbohaler (2.27 ± 0.39 μg) (See Table 2). Ivax

In conclusion, drug delivery from the Ivax MDPI is more uniform than that from the Oxis Turbuhaler but these devices produced a similar respirable dose of drug particles that may reach the site of actions in the airways.

## CONCLUSIONS.

Extensive work has been done in the development of the formulations employed in the Ivax formoterol MDPIs. Special attention has been paid to investigation of the effects of particle size distribution of the lactose, blending process and drug-to-carrier ratio on the dose uniformity and in vitro deposition profiles of the final blends.

A blend composed of 0.26% w/w micronised formoterol in the lactose were thus prepared using a Turbula Mixer. The final products were found to produce a mean drug per actuation within 80-120% label claim, mean fine particle dose expressed as percentage of label claim > 37%. All parameters met Pharmacopoeial specifications set up for dry powder inhalers. *The fine particle dose* of the Ivax Formoterol MDPIs, which relate directly to the therapeutic equivalence of these inhalers were comparable to the Oxis Turbohaler. The Ivax MDPI is shown to be more consistent in the delivery of formoterol than the Oxis Turbohaler.

CLAIMS:

1. A dry powder inhalation composition comprising particulate formoterol or a pharmaceutically acceptable derivative thereof as active ingredient and particulate lactose, wherein the lactose has a volume median diameter (VMD) of between 80 and 120 microns, 100% by weight of the lactose particles are less than 250 micron, between 80 and 96 % by weight are less than 150 microns, between 33 and 55% by weight are less than 90 micron and between 8 and 25% by weight are less than 5 micron.

2. A composition according to Claim 1, wherein between 25 and 37% by weight of the lactose are less than 60 microns.

3. A composition according to Claim 1 or 2, wherein between 15 and 35% by weight of the lactose are less than 30 microns.

4. A composition according to any one of the preceding Claims, wherein between 14 and 32% by weight of the lactose are less than 15 microns.

5. A composition according to any one of the preceding Claims, wherein between 13 and 30% by weight of the lactose are less than 10 microns.

6. A composition according to any one of the preceding Claims, wherein the between 34 and 52% by weight of the lactose are less than 90 microns.

7. A composition according to any one of the preceding Claims, wherein between 8.0 and 24.5% by weight of the lactose are less than 5 microns.

8. A composition according to any one of the preceding Claims, wherein between 18.5 and 36.5% by weight of the lactose are less than 60 microns.

9. A composition according to any one of the preceding Claims, wherein between 15.5 and 34.5% by weight of the lactose are less than 30 microns.

10. A composition according to any one of the preceding Claims, wherein between 14.5 and 31.5% by weight of the lactose are less than 15 microns.

11. A composition according to any one of the preceding Claims, wherein between 13.5 and 29.0% by weight of the lactose are less than 10 micron.

12. A composition according to any one of the preceding Claims, which contains between 0.01 and 10% by weight of active ingredient.

13. A composition according to any one of the preceding Claims, wherein the active ingredient is formoterol fumarate dihydrate.

The Patent Office
Concept House
Cardiff Road
Newport
South Wales
NP10 8QQ

the undersigned, being an officer duly authorised in accordance with Section 74(1) and (4) of e Deregulation & Contracting Out Act 1994, to sign and issue certificates on behalf of the mptroller-General, hereby certify that annexed hereto is a true copy of the documents as ginally filed in connection with the patent application identified therein.

so certify that the attached copy of the request for grant of a Patent (Form 1/77) bears an ndment, effected by this office, following a request by the applicant and agreed to by the ptroller-General.

cordance with the Patents (Companies Re-registration) Rules 1982, if a company named in ertificate and any accompanying documents has re-registered under the Companies Act with the same name as that with which it was registered immediately before re-registration or the substitution as, or inclusion as, the last part of the name of the words "public limited ny" or their equivalents in Welsh, references to the name of the company in this certificate y accompanying documents shall be treated as references to the name with which it is so tered.

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Signed A R Baskill

Dated 26 July 2006

Form 1/77

The Patent Office

22AUG02 E742803-4 D00032
P01/7700 0.00-0219514.7

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# Request for grant of a patent

*(See the notes on the back of this form. You can also get an explanatory leaflet from the Patent Office to help you fill in this form)*

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21 AUG 2002
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Cardiff Road
Newport
Gwent NP9 1RH

1. Your reference ~~GMW/RAC/P19583GB~~ 00390/GB

2. Patent application number
*(The Patent Office will fill in this part)*

0219514.7 21 AUG 2002

3. Full name, address and postcode of the or of each applicant *(underline all surnames)*

Norton Healthcare Limited
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Royal Docks
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E16 2QJ
United Kingdom

Patents ADP number *(if you know it)* 06887210003

If the applicant is a corporate body, give the country/state of its incorporation United Kingdom

4. Title of the invention

Inhalation Compositions Including Fine Carrier

5. Name of your agent *(if you have one)* ELKINGTON AND FIFE

"Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)*

ELKINGTON AND FIFE
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8 PEMBROKE ROAD
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TN13 1XR

Martin A. Hay
13 Queen Victoria St
Macclesfield
Cheshire
SK11 6LP

Patents ADP number *(if you know it)* 67004

pm 8/8/02

6. If you are declaring priority from one or more earlier patent applications, give the country and the date of filing of the or each of these earlier applications and *(if you know it)* the or each application number

| Country | Priority application number *(if you know it)* | Date of Filing *(day/month/year)* |
|---|---|---|
| N/A | | |

7. If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application

| Number of earlier application | Date of Filing *(day/month/year)* |
|---|---|
| N/A | N/A |

Form 1/77

Is a statement of inventorship and of right to grant of a patent required in support of this request? *(Answer "Yes" if:*
*a) any applicant named in part 3 is not an inventor, or*
*b) there is an inventor who is not named as an applicant, or*
*c) any named applicant is a corporate body.*

*See note (d))*

Yes

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| | |
|---|---|
| Priority documents | - |
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| Request for preliminary examination and search *(Patents Form 9/77)* | - |
| Request for substantive examination *(Patents Form 10/77)* | - |
| Any other documents *(please specify)* | - |

11. I/We request the grant of a patent on the basis of this application.

Signature: Elkington and Fife

Date: 21 August 2002

12. Name and daytime telephone number of person to contact in the United Kingdom

Dr Gordon Wright
01732 458881

# INHALATION COMPOSITIONS INCLUDING FINE CARRIER

This invention relates to dry powder inhalation compositions, their preparation and use. In particular, it is concerned with formulations of the medicament formoterol and pharmaceutically acceptable derivatives thereof mixed with particulate lactose.

In order to be able to be inspired into the key target sites in the lungs of patients, inhalation drugs are typically provided in micronized form with average particle sizes of up to 10 microns. A number of devices have been developed for assisting the delivery of such medicaments into the lungs of patients. In one sort of device, a dry powdered inhaler (DPI) device, the medicament to be inhaled is dispensed into an air stream produced by the inspiratory action of the patient. A large number of such devices have been developed. The device may be a single dose device (eg wherein drug is dispensed from a pre-metered dosage means such as a capsule) or multidose (where the drug is stored in a reservoir and then metered prior to dispersal in the air stream or the drug is pre-metered and stored in multiple dosage packs such as blisters). In many (but not all) DPI devices, the particulate drug is mixed with an excipient powder of larger average particle size and the drug particles are blended with the excipient to create a generally homogenous mixture. The larger particle size of the excipient results in the powder mixture being flowable, and the homogeneity of the mixture enables it to be metered into accurately measurable doses. This is of particular importance when only very small quantities of the drug are required in a dose. Excipient powders of this kind, pharmaceutical powder compositions for inhalation utilising such excipients are described, for example, in US Patent 3 957 965.

The accurate metering of highly potent inhalable drugs causes particular problems, as the quantity of medicament in the composition relative to that of the carrier is likely to be particularly small. (Less than 1 part of drug to 50 parts of carrier). One such medicament is formoterol which is often administered to patients at a dose of less than 60 micrograms; doses may be as small as 6 micrograms. We have now found dry powder inhalation compositions of formoterol which are easier to handle than previously described compositions. In addition, the composition can be readily filled into reservoir containing multidose DPI devices, such as the DPI device described in WO 92/10229. In addition, such compositions can be accurately metered and give

better dispersions when dispensed from such devices, then previously described compositions. Certain compositions may also be more stable.

According to the invention, we provide a dry powder inhalation composition comprising particulate formoterol or a pharmaceutically acceptable derivative thereof as active ingredient and particulate lactose, wherein the lactose has a volume mean diameter (VMD) of between 70 and 80 microns, 100% by weight of the lactose particles are less than 150 microns, between 75 and 85 % by weight are less than 90 microns and between 6 and 8 % by weight are less than 5 microns.

We prefer compositions in which between 25 and 33 %, more preferably between 27 and 31 %, by weight of the lactose has a particle size less than 60 microns. A particular range that may be mentioned is 28 to 31 % by weight.

We prefer compositions wherein between 12 and 20 % by weight, more preferably between 14 and 17.5 % by weight, of the lactose has a particle size less than 30 microns. A particular range that may be mentioned is between 14.4 and 17 % by weight.

We prefer a composition wherein between 11 and 18 % by weight, more preferably 12.5 and 15 % by weight of the lactose has a particle size less than 15 microns. A particularly preferred range that may be mentioned is between 12.7 and 14.8 %.

We prefer compositions wherein between 8 and 15 % by weight, more preferably between 10.5 and 12.5 % by weight of the lactose has a particle size less than 10 microns. A particularly preferred range is between 10.7 and 12.4 %.

We prefer compositions wherein between 77 and 83 % by weight of the lactose has a particle size less than 90 microns, more preferably between 77.5 and 80 % by weight.

We prefer compositions in which between 6.5 and 7.5 % by weight, more particularly between 6.6 and 7.4 % by weight of the lactose has a particle size less than 5 microns.

The compositions of the present invention may be used in the treatment of chronic obstructive pulmonary disease.

The active ingredient may be in any isomeric form or mixture of isomeric forms, for example a pure enantiomer, particularly the R, R-enantiomer, a mixture of enantiomers, a racemate or a mixture thereof. Pharmaceutically acceptable derivatives of formoterol include pharmaceutically acceptable salts, in particular acid addition salts with inorganic acids such as hydrochloric acid, hydrobromic acid, sulphuric or phosphoric acid. The salt may also be with an organic acid such as acetic, succinic, maleic, furmaric, citric, tartaric, lactic or benzoic. The active ingredient and pharmaceutically acceptable derivatives thereof may exist in the form of a solvate, in particular a hydrate. A preferred form of active ingredient for use in the invention is formoterol fumarate, especially formoterol fumarate di-hydrate, conveniently in its racemic form. Formoterol, salts and hydrates thereof and salt hydrates thereof as described above may be prepared by known methods, for example as described in US 3 994 974 or US 5 684 199.

In general, the active ingredient is present in the dry powder composition at an amount which is less than 10 %, preferably less than 2 % and most preferably less than 1 %. The actual amount of active ingredient in the composition will depend to a large extent on the nature of the dry powder inhaler and the quantity of composition that is metered for each individual dose. Where a large dose of composition is metered, the proportion of formoterol in the dose will be reduced. Particularly dilute compositions are disclosed in WO 01/39745, for example 0.02 % by weight.

The mean particle diameter of the active ingredient is preferably up to 10 microns, more preferably up to 5 microns, especially from 1 to 5 microns. The particle size of the active ingredient can be reduced to the desired level by conventional means, for example by grinding in a mill for example an air jet, ball or vibrator mill, by sieving, by crystallisation, by spray-drying or by lyophilisation.

The desired particle size distribution of the lactose may be prepared in a similar way. However, it is preferable to prepare the lactose by blending two or more portions of

previously classified lactose, for example a fine blend of lactose, in which the mean particle diameter is less than 10 microns and a portion in which the mean particle diameter is relatively coarse. A characteristic coarse lactose is that supplied as classified lactose that is collected on a mesh with mesh size of 63 microns after passing through a mesh with mesh size of 90 microns.

The dry powder composition may be metered and filled into capsules, eg gelatine or hydroxypropyl methol cellulose capsules such that the capsule contains a unit dose of active ingredient.

Doses of active ingredient to be held in accordance with the invention, may be in general from 1 to 60 micrograms. When the active ingredient is formoterol fumarate dihydrate, the dose may be, for example, from 6 to 54 micrograms. Preferred doses are from 6 to 24 micrograms, especially the unit doses of 6 micrograms, 12 micrograms and 24 micrograms. These doses may be administered once or twice daily.

When the dry powder is in a capsule containing a unit dose of active ingredient, the total amount of composition will depend on the size of the capsules and the characteristics of the inhalation device with which the capsules are being used. However, characteristic total fill weights of dry powder to per capsule are between 1 and 25 mg eg 5, 10, 15 or 20 mg.

Alternatively, the dry powder composition according to the invention may be filled into the reservoir of a multidose dry powder inhaler (MDPI), for example of the kind illustrated in WO 92/10229.

Compositions according to the invention may be readily prepared by blending the required amount of active ingredient with the required amount of particulate lactose of the desired particle size distribution.

Preferably, the lactose is alpha lactose monohydrate.

**Example 1**

0.265 grams of formoterol (as the fumarate dihydrate salt) was blended with 99.735 grams of lactose that has a particle size distribution within the range shown in Table 1. The lactose was prepared by blending a mixture of 63 to 90 micron lactose (97.5%) with microfine lactose having a VMD of 7.5 microns (2.5%). The formoterol lactose blend was filled into the reservoir of a MDPI device of the type illustrated in WO 92/10229.

**Table 1**: Particle size distributions for lactose with a broad particle size distribution

| **Parameters** | Mean | Range |
|---|---|---|
| VMD | 76.9 μm | 75.8 – 77.5 μm |
| GSD | 1.6 | 1.5 –1.9 |
| < 5 μm | 7.0 % | 6.7% - 7.3% |
| < 10 μm | 11.7% | 10.9% - 12.3% |
| < 15 μm | 13.8% | 12.9% - 14.6% |
| < 30 μm | 15.7% | 14.6% - 16.6% |
| < 60 μm | 29.3% | 28.3% - 30.6% |
| < 90 μm | 78.6% | 77.8% - 79.5% |
| > 150 μm | 100% | 100% |

The inhalers that contained the formulation were then tested for pharmaceutical performance under conditions specified in European Pharmacopoeia (2001). The drug per actuation (DPA) was measured using a dose unit sampling unit whilst fine particle dose (FPD) and fine particle fraction (FPF) were measured using a 5-stage liquid impinger

The compositions gave excellent dose uniformity with relative standard deviation (RSD) of delivered doses ranging from 4-13% (Table 2) when used in association with the device of WO 92/10229, with a good proportion of fine particles of the drug (Table

3). The pharmaceutical performance of the inhalers remain stable after exposure unprotected to elevated conditions.

**Table 2.** Relative standard deviation (RSD) of ten doses (3 at beginning, 4 at middle and 3 at end of device life) from each inhaler device containing a formulation using the said lactose as the excipient before and after storage unprotected at 25°C/60% RH for a month

| Before storage | | | After storage | | |
|---|---|---|---|---|---|
| Device 1 | Device 2 | Device 3 | Device 1 | Device 2 | Device 3 |
| **8.1%** | **7.9%** | **11.4%** | **12.8%** | **10.5%** | **4.7%** |

**Table 3.** Fine particle fraction (FPF, % recovered dose) of formoterol from each inhaler device containing a formulation using the said lactose as excipient before and after storage unwrapped at 25°C/60% RH for a month.

| **Parameters** | **Before storage** | | | **After storage** | | |
|---|---|---|---|---|---|---|
| | Device 1 | Device 2 | Device 3 | Device 1 | Device 2 | Device 3 |
| Beginning of device life | **38** | **40** | **40** | **41** | **39** | **39** |
| **End of device life** | **38** | **38** | **42** | **40** | **35** | **43** |

CLAIMS:

1. A dry powder inhalation composition comprising particulate formoterol or a pharmaceutically acceptable derivative thereof as active ingredient and particulate lactose, wherein the lactose has a volume mean diameter (VMD) of between 70 and 80 microns, 100% by weight of the lactose particles are less than 150 micron, between 75 and 85% by weight are less than 90micron and between 6 and 8% by weight are less than 5 micron.

2. A composition according to Claim 1, wherein between 25 and 33% by weight of the lactose are less than 60 microns.

3. A composition according to Claim 1 or 2, wherein between 12 and 20% by weight of the lactose are less than 30 microns.

4. A composition according to any one of the preceding Claims, wherein between 11 and 18% by weight of the lactose are less than 15microns.

5. A composition according to any one of the preceding Claims, wherein between 8 and 15% by weight of the lactose are less than 10 microns.

6. A composition according to any one of the preceding Claims, wherein the between 77 and 83% by weight of the lactose are less than 90 microns.

7. A composition according to any one of the preceding Claims, wherein between 6.5 and 7.5% by weight of the lactose are less than 5 microns.

8. A composition according to any one of the preceding Claims, wherein between 27 and 31% by weight of the lactose are less than 60 microns.

9. A composition according to any one of the preceding Claims, wherein between 14 and 17.5% by weight of the lactose are less than 30 microns.

10. A composition according to any one of the preceding Claims, wherein between 12.5 and 15% by weight of the lactose are less than 15 microns.

11. A composition according to any one of the preceding Claims, wherein between 10.5 and 12.5% by weight of the lactose are less than 10 micron.

12. A composition according to any one of the preceding Claims, which contains between 0.01 and 10% by weight of active ingredient.

13. A composition according to any one of the preceding Claims, wherein the active ingredient is formoterol fumarate dihydrate.